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Drug treatment

Retina. 2016 Jul 4. [Epub ahead of print]

METAANALYSIS OF REAL-WORLD OUTCOMES OF INTRAVITREAL RANIBIZUMAB FOR THE TREATMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Kim LN, Mehta H, Barthelmes D, Nguyen V, Gillies MC.

PURPOSE: To report the efficacy and safety of intravitreal ranibizumab for neovascular age-related macular degeneration (nAMD) in real-world practice.

METHODS: Metaanalysis of ~26,360 patients from 42 real-world observational studies reporting outcomes of intravitreal ranibizumab for nAMD published between 2007 and 2015. Baseline demographics, lesion type, and visual acuity (VA) were recorded. The weighted mean was calculated for change in VA and frequency of injections and visits during year 1, year 2, and ≥3 years. Local and systemic adverse events were recorded.

RESULTS: The mean change in VA for patients receiving a treat-and-extend regimen was +8.8 (95% confidence interval [CI]: 5.8 to 11.8), +6.7 (95% CI: 3.2 to 10.1), and +5.4 (95% CI: -4.1 to 14.9) Early Treatment Diabetic Retinopathy Study (ETDRS) letters at 1 year (n = 1,539), 2 years (n = 2,521), and ≥3 years (n = 1,298), in comparison with +3.5 (95% CI: 2.0 to 5.0), +1.3 (95% CI: -1.6 to 4.2), and -1.9 (95% CI: -9.8 to 6.0) ETDRS letters for pro re nata at 1 year (n = 20,247), 2 years (n = 14,408), and ≥3 years (n = 11,714). Treat-and-extend patients received on average more injections (6.9 vs. 4.7) but had fewer visits (7.6 vs. 9.2) in the first year. Baseline characteristics were similar between the regimens. The reported rate of endophthalmitis was 17 of 66,176 intravitreal injections (0.026%).

CONCLUSION: Intravitreal ranibizumab for nAMD prevents severe visual loss in real-world practice. Patients can achieve visual gain from baseline, but the extent to which these are maintained in the long term may depend on the frequency of injections.

PMID: 27388744

Retina. 2016 Jul 1. [Epub ahead of print]

RETICULAR PSEUDODRUSEN ARE NOT A PREDICTIVE FACTOR FOR THE 1-YEAR RESPONSE TO INTRAVITREAL RANIBIZUMAB IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Nghiem-Buffet S, Giocanti-Auregan A, Jung C, Dubois L, Dourmad P, Galbadon L, Fajnkuchen F, Quentel G, Cohen SY.

PURPOSE: To investigate reticular pseudodrusen (RPD) as a potential baseline factor predictive of a poor 1-year response to intravitreal ranibizumab in eyes with neovascular age-related macular degeneration.

METHODS: Retrospective, monocentric case series including 98 consecutive naive neovascular age-related macular degeneration patients. Presence of RPD was assessed by two graders based on color, blue-light, fundus autofluorescence pictures, and spectral-domain optical coherence tomography. A correlation between the presence of RPD and the visual change was investigated. Other baseline characteristics studied in a monovariate and multivariate analysis were the following: age, gender, affected side, loading dose, type of neovascularization, presence of retinal pigment epithelial detachment >250 µm, subretinal or intraretinal fluid, blood over >50% of the lesion, and subfoveal choroidal thickness.

RESULTS: The presence of RPD was not associated with a visual change ($P = 0.96$), but with a thin subfoveal choroidal thickness at baseline ($P < 0.0001$). The monovariate analysis showed that the presence of blood at baseline was associated with visual gain ($P = 0.007$).

CONCLUSION: The presence of RPD at baseline was not identified as a factor associated with a poor 1-year response to ranibizumab in eyes with neovascular age-related macular degeneration. Studies with a longer follow-up may be needed to assess the impact of RPD on the visual prognosis of eyes with neovascular age-related macular degeneration.

PMID: 27380430

Clin Ophthalmol. 2016 Jun 21;10:1161-5. eCollection 2016.

Twelve-month outcomes in patients with retinal vein occlusion treated with low-frequency intravitreal ranibizumab.

Sakanishi Y, Lee A, Usui-Ouchi A, Ito R, Ebihara N.

PURPOSE: The purpose of this study was to determine the clinical efficacy of low-frequency intravitreal ranibizumab to treat macular edema due to retinal vein occlusion (RVO).

PATIENTS AND METHODS: This was a retrospective examination of cases that received intravitreal ranibizumab for untreated RVO over a period of 12 months. Instead of the conventional three monthly injections, injections were given once during the introductory period. If the recurrence of macular edema was diagnosed during the monthly visit, additional injections were given as needed. There were 21 eyes of 21 patients with branch RVO (BRVO) and ten eyes of ten patients with central RVO (CRVO). The parameters examined included the number of injections over the 12-month period, improvements in best-corrected visual acuity (BCVA), and the central macular thickness (CMT). For BRVO, preinjection parameters that had an effect on the prognosis of BCVA after the 12-month period were also examined.

RESULTS: The total mean number of injections over the 12-month period was 3.4 for CRVO and 2.1 for BRVO. For CRVO, the BCVA in log minimum angular resolution changed from a preinjection value of 0.80 to 0.55 at 12 months. For BRVO, the change was from 0.51 to 0.30. For all diseases, BCVA improved after 12 months compared with the preinjection values ($P < 0.05$). There was improvement in the CMT, and the CRVO changed from 765.0 µm at preinjection to 253.5 µm 12 months later. BRVO changed from 524.1 to 250.1 µm, and pre-injection BCVA was associated with a prognosis of visual acuity after 12 months of the initial injection ($P = 0.0485$).

CONCLUSION: Even with a low number of injections during the introductory period, there were still improvements in both visual acuity and CMT in RVO patients after 12 months, indicating that it was an effective treatment.

PMID: 27382250 PMCID: PMC4922787

Clin Ophthalmol. 2016 Jun 17;10:1131-8. eCollection 2016.

Effect of prophylactic timolol 0.1% gel on intraocular pressure after an intravitreal injection of ranibizumab: a randomized study.

Pece A, Allegrini D, Montesano G, Dimastrogiovanni AF.

PURPOSE: The purpose of this study is to make a prospective evaluation of the effect of timolol 0.1% eye gel on short-term intraocular pressure (IOP) after an intravitreal injection (IVI) of ranibizumab.

PARTICIPANTS AND METHODS: One hundred and fifty eyes of 150 IVI-naïve patients with macular edema caused by various pathological conditions (age-related macular degeneration, central or branch retinal vein occlusion, and diabetic retinopathy) were scheduled to undergo an IVI of ranibizumab (0.5 mg/0.05 cc). The patients were randomly divided into three groups: 50 were not treated with timolol before the IVI (group 1); 50 received an instillation of timolol 0.1% eye gel the evening before the IVI (group 2); and 50 received an instillation of timolol 0.1% eye gel 2 hours before the IVI (group 3). The incidence of clinically significant intraocular hypertensive spikes (>25 mmHg and >40 mmHg) was then assessed.

RESULTS: Our findings showed that mean IOP at baseline was significantly higher than at both 5 and 60 minutes after IVI ($P < 0.01$). Spikes of >25 mmHg were recorded at either time in 27 patients (54%) in group 1, 23 patients (44%) in group 2, and 24 patients (48%) in group 3. None of the between-group differences were significant. Spikes of >40 mmHg (which were only detected 5 minutes after IVI) were recorded in nine (18%), eight (16%), and one patient (2%) in groups 1, 2, and 3, respectively. The only significant difference was between the control and group 3 ($P = 0.012$).

CONCLUSION: An increase in IOP after antivascular endothelial growth factor IVI is a frequent complication. The prophylactic use of timolol 0.1% gel effectively reduced the mean IOP when administered 2 hours before IVI and was also effective in preventing dangerous IOP spikes of >40 mmHg. It is therefore recommended before IVIs as a means of preventing emergency procedures and preserving the health of the optic nerve.

PMID: 27382246 PMCID: PMC4918739

Sci Rep. 2016 Jul 8;6:29445.

Microaneurysms cause refractory macular edema in branch retinal vein occlusion.

Tomiyasu T, Hirano Y, Yoshida M, Suzuki N, Nishiyama T, Uemura A, Yasukawa T, Ogura Y.

Abstract: Intravitreal anti-vascular endothelial growth factor (VEGF) agents can treat macular edema (ME) in branch retinal vein occlusion (BRVO). However, refractory ME, the mechanism of which is not well elucidated, occurs frequently. Sixty-six eyes with ME secondary to BRVO were enrolled in this retrospective observational case-control study. Twenty eyes received a sub-Tenon's capsule injection of triamcinolone acetonide (STTA), 22 eyes an intravitreal anti-VEGF injection (ranibizumab), 16 eyes were switched from STTA to ranibizumab, 4 eyes underwent vitrectomy, and 4 eyes were untreated. Multiple regression analysis and multivariate logistic regression analysis were conducted, respectively, to identify independent predictors of visual acuity (VA) prognosis and risk factors for refractory ME longer than 1 year. The mechanism of refractory ME and therapeutic approaches for identified risk factors also were investigated. Thirty-four (52%) eyes had refractory ME for over 1 year. Microaneurysms were identified as risk factors for refractory ME, leading to poor final VA. Ranibizumab suppressed microaneurysm formation and refractory ME, with early administration more effective. For already formed microaneurysms, laser photocoagulation reduced additional treatments. Microaneurysms may cause refractory ME in BRVO. Alternative therapy to suppress microaneurysms should be considered to prevent refractory ME in patients with BRVO.

PMID: 27389770

Other treatment & diagnosis

Retina. 2016 Jul 6. [Epub ahead of print]

LONGITUDINAL STRUCTURAL CHANGES IN LATE-ONSET RETINAL DEGENERATION.

Cukras C, Flamendorf J, Wong WT, Ayyagari R, Cunningham D, Sieving PA.

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PURPOSE: To characterize longitudinal structural changes in early stages of late-onset retinal degeneration to investigate pathogenic mechanisms.

METHODS: Two affected siblings, both with a S163R missense mutation in the causative gene C1QTNF5, were followed for 8+ years. Color fundus photos, fundus autofluorescence images, near-infrared reflectance fundus images, and spectral domain optical coherence tomography scans were acquired during follow-up.

RESULTS: Both patients, aged 45 and 50 years, had good visual acuities (>20/20) in the context of prolonged dark adaptation. Baseline color fundus photography demonstrated yellow-white, punctate lesions in the temporal macula that correlated with a reticular pattern on fundus autofluorescence and near-infrared reflectance imaging. Baseline spectral domain optical coherence tomography imaging revealed subretinal deposits that resemble reticular pseudodrusen described in age-related macular degeneration. During follow-up, these affected areas developed confluent thickening of the retinal pigment epithelial layer and disruption of the ellipsoid zone of photoreceptors before progressing to overt retinal pigment epithelium and outer retinal atrophy.

CONCLUSION: Structural changes in early stages of late-onset retinal degeneration, revealed by multimodal imaging, resemble those of reticular pseudodrusen observed in age-related macular degeneration and other retinal diseases. Longitudinal follow-up of these lesions helps elucidate their progression to frank atrophy and may lend insight into the pathogenic mechanisms underlying diverse retinal degenerations.

PMID: 27388725

Retin Cases Brief Rep. 2016 Jul 1. [Epub ahead of print]

INCIDENCE OF ACUTE EXUDATIVE MACULOPATHY AFTER REDUCED-FLUENCE PHOTODYNAMIC THERAPY.

Mammo Z, Forooghian F.

PURPOSE: To describe the incidence and features of acute exudative maculopathy (AEM) after half-fluence photodynamic therapy (PDT) and/or very minimal fluence PDT.

METHODS: Retrospective chart review of all patients treated over a 7-year period.

RESULTS: A total of 52 patients (58 eyes, 140 treatments) were treated with half-fluence PDT and/or very minimal fluence PDT. Patients were diagnosed with either central serous chorioretinopathy (CSCR) or neovascular age-related macular degeneration (nAMD). Two patients (1 CSCR and 1 nAMD) returned to the clinic with acute vision loss after treatment and were identified as having developed AEM. In the CSCR case, resolution occurred after intravitreal bevacizumab treatment. The nAMD case resolved with topical difluprednate treatment. We were unable to identify any risk factors for the development of AEM.

CONCLUSION: AEM seems to be a rare (incidence 1.4% per treatment) and unpredictable reaction related to the proinflammatory effects of half-fluence PDT and very minimal fluence PDT. Because of the inherent limitations of this study, the true incidence of AEM after reduced-fluence PDT may be higher.

PMID: 27380223

Am J Ophthalmol. 2016 Jul 6. [Epub ahead of print]

Optical coherence tomography angiography: a useful tool for diagnosis of treatment-naïve quiescent choroidal neovascularization.

Carnevali A, Cicinelli MV, Capuano V, Corvi F, Mazzaferro A, Querques L, Scordia V, Souied EH, Bandello F, Querques G.

PURPOSE: To describe the optical coherence tomography angiography (OCT-A) features of treatment-naïve quiescent choroidal neovascularization (CNV) secondary to age-related macular degeneration, and to estimate the detection rate for neovascularization by means of OCT-A.

DESIGN: Diagnostic tool validity assessment.

METHODS: Treatment-naïve quiescent CNV were identified from a pool of patients at 2 retina referral centers. Patients underwent a complete ophthalmologic examination including fluorescein angiography, indocyanine green angiography, spectral-domain OCT and OCT-A. Detection rates of CNV by means of OCT-A were estimated with a second cohort of patients without CNV (negative controls) **RESULTS:** Twenty-two eyes of 20 consecutive patients with quiescent CNV were included. In 4 out of 22 eyes it was not possible to classify the CNV "shape", "core", "margin", and "location" either because the vascular network was not clearly shown (3 cases) or because it was not visible at all (1 case). CNV shape on OCT-A was rated as circular in 8 eyes and irregular in 10 eyes. CNV core was visible in 2 eyes. CNV margin was considered as well-defined in 15 eyes, and poorly-defined in 3 eyes. CNV margin showed small loops in 9 eyes and large loops in the other 6 eyes. CNV location was foveal-sparing in 12 eyes. Sensitivity and specificity of quiescent CNV detection by OCT-A turned out to be 81.8% and 100%, respectively.

CONCLUSIONS: OCT-A allows the clinician to identify noninvasively treatment-naïve quiescent CNV and may possibly be considered as a useful tool to guide the frequency of return visits and possibly make treatment decisions.

PMID: 27394033

Oncotarget. 2016 Jul 6. [Epub ahead of print]

Cell surgery and growth factors in dry age-related macular degeneration: visual prognosis and morphological study.

Limoli PG, Limoli C, Vingolo EM, Scalinci SZ, Nebbioso M.

BACKGROUND: The aim of this research was to study the overall restoration effect on residual retinal cells through surgically grafted autologous cells onto the surrounding tissue, choroid and retina in order to produce a constant secretion of growth factors (GFs) in dry age-related macular degeneration (AMD) patients.

RESULTS: 6 months after surgery, several values were statistically significant in the group with higher RTA. Also patient compliance analysis (PCA) in relation to functional change perception appeared to be very good.

METHODS: Thirty-six eyes of 25 patients (range 64-84 years of age) affected by dry AMD were included in study, and divided in two groups by spectral domain-optical coherence tomography (SD-OCT): group A with retinal thickness average (RTA) less than 250 microns (μm) and group B with RTA equal to or more than 250 μm . Adipocytes, adipose-derived stem cells from the stromal-vascular fraction, and platelets from platelet-rich plasma were implanted in the suprachoroidal space. Particularly, the following parameters were evaluated: best corrected visual acuity (BCVA) for far and near distance, retinal thickness maps, scotopic and photopic electroretinogram (ERG), and microperimetry (MY). All statistical analyses were performed with STATA 14.0 (Collage Station, Texas, USA).

CONCLUSIONS: The available set of GFs allowed biological retinal neuroenhancement. After 6 months it improved visual performance (VP), but the increase was better if RTA recorded by OCT was higher, probably in relation to the presence of areas with greater cellularity.

PMID: 27391437

Arch Soc Esp Oftalmol. 2016 Jul 1. [Epub ahead of print]

Implications of the anatomical classification of the neovascular form of age-related macular degeneration. [Article in English, Spanish]

Gallego-Pinazo R, Monje-Fernández L, García-Marín N, Andreu-Fenoll M, Dolz-Marco R.

OBJECTIVE: To present the clinical relevance of the anatomical classification of the neovascular form of Age-Related Macular Degeneration (AMD).

METHODS: Critical analysis of the current situation in the management of patients with neovascular AMD, by reviewing the available scientific evidence with regards to the classification of the types of neovascular lesion by angiography and optical coherence tomography (OCT).

RESULTS: The classification of the neovascular lesion type secondary to AMD by OCT in type 1 lesions (under the pigment epithelium), type 2 (subretinal), and type 3 (retinal angiomatous proliferation), provides an added value in allowing to establish a long-term visual prognosis, an estimate of the number of treatments that a certain case may require, and a stratification of the risk for secondary geographic atrophy.

CONCLUSIONS: Incorporating OCT to the initial qualitative analysis of cases with neovascular AMD offers an added value superior to that provided by the angiography, with the relevant clinical implications.

PMID: 27378456

Arch Soc Esp Oftalmol. 2016 Jul 4. [Epub ahead of print]

Multimodal imaging in neovascular Age-Related Macular Degeneration. [Article in English, Spanish]

Gallego-Pinazo R, Andreu-Fenoll M, García-Marín N, Dolz-Marco R.

PMID: 27388110

Ophthalmol Eye Dis. 2016 Jun 23;8:23-30. eCollection 2016.

Targeting MAPK Signaling in Age-Related Macular Degeneration.

Kyosseva SV.

Abstract: Age-related macular degeneration (AMD) is a major cause of irreversible blindness affecting elderly people in the world. AMD is a complex multifactorial disease associated with demographic, genetics, and environmental risk factors. It is well established that oxidative stress, inflammation, and apoptosis play critical roles in the pathogenesis of AMD. The mitogen-activated protein kinase (MAPK) signaling pathways are activated by diverse extracellular stimuli, including growth factors, mitogens, hormones, cytokines, and different cellular stressors such as oxidative stress. They regulate cell proliferation, differentiation, survival, and apoptosis. This review addresses the novel findings from human and animal studies on the relationship of MAPK signaling with AMD. The use of specific MAPK inhibitors may represent a potential therapeutic target for the treatment of this debilitating eye disease.

PMID: 27385915 PMCID: PMC4920203

Pathogenesis

J Pathol. 2016 Jul 4. [Epub ahead of print]

Monomeric C-reactive protein and inflammation in Age-related Macular Degeneration The role of monomeric C-reactive protein in AMD.

Chirco KR,² Scott Whitmore S, Wang K, Potempa LA, Halder JA, Stone EM, Tucker BA, Mullins RF.

Abstract: Age-related macular degeneration (AMD) is a devastating disease characterized by central vision loss in elderly individuals. Previous studies have suggested a link between elevated levels of total C-reactive protein (CRP) in the choroid, CFH genotype, and AMD status; however, the structural form of CRP present in the choroid, its relationship to CFH genotype, and its functional consequences have not been assessed. In this report, we studied genotyped human donor eyes ($n = 60$) and found that eyes homozygous for the high-risk CFH (Y402H) allele had elevated monomeric CRP (mCRP) within the choriocapillaris and Bruch's membrane, compared to those with the low-risk genotype. Treatment of choroidal endothelial cells in vitro with mCRP increased migration rate and monolayer permeability compared to treatment with pCRP or medium alone. Organ cultures treated with mCRP exhibited dramatically altered expression of inflammatory genes as assessed by RNA sequencing, including ICAM-1 and CA4, both of which were confirmed at the protein level. Our data indicate that mCRP is the more abundant form of CRP in human choroid, and that mCRP levels are elevated in individuals with the high-risk CFH genotype. Moreover, pro-inflammatory mCRP significantly affects endothelial cell phenotypes in vitro and ex vivo, suggesting a role for mCRP in choroidal vascular dysfunction in AMD.

PMID: 27376713

Sci Rep. 2016 Jul 4;6:29046.

Transcriptome Analysis on Monocytes from Patients with Neovascular Age-Related Macular Degeneration.

Grunin M, Hagbi-Levi S, Rinsky B, Smith Y, Chowers I.

Abstract: Mononuclear phagocytes (MPs), including monocytes/macrophages, play complex roles in age-related macular degeneration (AMD) pathogenesis. We reported altered gene-expression signature in peripheral blood mononuclear cells from AMD patients, and a chemokine receptor signature on AMD monocytes. To obtain comprehensive understanding of MP involvement, particularly in peripheral circulation in AMD, we performed global gene expression analysis in monocytes. We separated monocytes from treatment-naïve neovascular AMD (nvAMD) patients ($n = 14$) and age-matched controls ($n = 15$), and performed microarray and bioinformatics analysis. Quantitative real-time PCR was performed on other sets of nvAMD ($n = 25$), atrophic AMD ($n = 21$), and controls ($n = 28$) for validation. This validated microarray genes (like TMEM176A/B and FOSB) tested, including differences between nvAMD and atrophic AMD. We identified 2,165 differentially-expressed genes ($P < 0.05$), including 79 genes with log2 fold change ≥ 1.5 between nvAMD and controls. Functional annotation using DAVID and TANGO demonstrated immune response alterations in AMD monocytes ($\text{FDR-}P < 0.05$), validated by randomized data comparison ($P < 0.0001$). GSEA, ISMARA, and MEME analysis found immune enrichment and specific involved microRNAs. Enrichment of differentially-expressed genes in monocytes was found in retina via SAGE data-mining. These genes were enriched in non-classical vs. classical monocyte subsets ($P < 0.05$). Therefore, global gene expression analysis in AMD monocytes reveals an altered immune-related signature, further implicating systemic MP activation in AMD.

PMID: 27374485 PMCID: PMC4931446

Sci Rep. 2016 Jul 4;6:28993.

Differential expression of microRNAs in retinal vasculopathy caused by selective Müller cell disruption.

Chung SH, Gillies M, Yam M, Wang Y, Shen W.

Abstract: Vascular changes and photoreceptor degeneration are features of age-related macular degeneration, diabetic retinopathy and macular telangiectasis. We have profiled the differential expression of microRNAs and analysed their target genes in transgenic mice in which induced Müller cell disruption

results in photoreceptor degeneration, vascular leak and deep retinal neovascularisation. We identified 9 miRNAs which were differentially expressed during the development of retinal neovascularization and chose miR-200b and its target genes for further study. Using qRT-PCR and western blot analysis, we found that downregulation of miR-200b was negatively correlated with its target genes, including zinc finger E-box binding homeobox (ZEB) 1 and 2 and vascular endothelial growth factor receptor 1. Double immunofluorescence labelling revealed that the newly formed vessels in the outer retina were positive for ZEB2. Furthermore, intravitreal injections of a miR-200b-mimic and anti-miR-200b confirmed the negative correlation of miR-200b and its target gene expression. We also found that the miR-200b-mimic inhibited vascular leak in the established mild vascular lesions, whereas anti-miR-200b promoted it. Taken together, these data suggest that miR-200b may play a role in the development of intraretinal neovascularisation.

PMID: 27373709 PMCID: PMC4931578

Histochem Cell Biol. 2016 Jul 2. [Epub ahead of print]

Epithelial-mesenchymal transition of the retinal pigment epithelium causes choriocapillaris atrophy.

Ohlmann A, Scholz M, Koch M, Tamm ER.

Abstract: Epithelial-to-mesenchymal transition (EMT) of the retinal pigment epithelium (RPE) is commonly observed at sites of choroidal neovascularization in patients suffering from age-related macular degeneration. To learn in an experimental model how RPE EMT affects the biology of the choroidal vasculature, we studied transgenic mice (β B1-TGF- β 1) with ocular overexpression of transforming growth factor- β 1 (TGF- β 1). RPE EMT was detectable at postnatal day (P)1 and included marked structural and functional alterations such as loss of the outer blood-retina barrier and reduced mRNA expression of the RPE-characteristic molecules Rbp1, Rpe65, Rbp1 and Vegfa. Moreover, vascular endothelial growth factor (VEGF) was not detectable by immunohistochemistry at the RPE/choroid interface, while RPE cells stained intensely for α -smooth muscle actin. The choriocapillaris, the characteristic choroidal capillary network adjacent to the RPE, developed normally and was not obviously changed in embryonic transgenic eyes but was absent at P1 indicating its atrophy. At around the same time, photoreceptors stopped to differentiate and photoreceptor apoptosis was abundant in the second week of life. Structural changes were also seen in the retinal vasculature of transgenic animals, which did not form intraretinal vessels, and the hyaloid vasculature, which did not regress. In addition, the amounts of retinal HIF-1 α and its mRNA were markedly reduced. We conclude that high amounts of active TGF- β 1 in the mouse eye cause transdifferentiation of the RPE to a mesenchymal phenotype. The loss of epithelial differentiation leads to the diminished synthesis of RPE-characteristic molecules including that of VEGF. Lack of RPE-derived VEGF causes atrophy of the choriocapillaris, a scenario that disrupts photoreceptor differentiation and finally results in photoreceptor apoptosis. Lack of retinal vessel formation and of hyaloid vessel regression might be caused by the decrease in the metabolic requirements of the neuroretina leading to low amounts of retinal HIF-1 α . In summary, our data indicate that failure of RPE differentiation may well precede and cause atrophy of the choriocapillaris. In contrast, RPE EMT is not sufficient to cause choroidal neovascularization.

PMID: 27372654

Redox Biol. 2016 Jun 20;9:50-56. [Epub ahead of print]

Artemisinin protects human retinal pigment epithelial cells from hydrogen peroxide-induced oxidative damage through activation of ERK/CREB signaling.

Chong CM, Zheng W.

Abstract: The pathological increase in the levels of reactive oxygen species (ROS) in the retinal pigment epithelium (RPE), is implicated in the development of age-related macular degeneration (AMD). The discovery of drug candidates to effectively protect RPE cells from oxidative damage is required to resolve the pathological aspects and modify the process of AMD. In this study, a FDA-approved anti-malaria drug, Artemisinin was found to suppress hydrogen peroxide (H₂O₂)-induced cell death in human RPE cell-D407 cells. Further study showed that Artemisinin significantly suppressed H₂O₂- induced D407 cell death by

restoring abnormal changes in nuclear morphology, intracellular ROS, mitochondrial membrane potential and apoptotic biomarkers. Western blotting analysis showed that Artemisinin was able to activate extracellular regulated ERK/CREB survival signaling. Furthermore, Artemisinin failed to suppress H₂O₂-induced cytotoxicity and the increase of caspase 3/7 activity in the presence of the ERK inhibitor PD98059. Taken together, these results suggest that Artemisinin is a potential protectant with the pro-survival effects against H₂O₂ insult through activation of the ERK/CREB pathway.

PMID: 27372058

Eur J Pharmacol. 2016 Jul 4. [Epub ahead of print]

Glucocorticoid Therapy and ocular hypertension.

Dibas A, Yorio T.

Abstract: The projected number of people who will develop age-related macular degeneration is estimated at 2020 is 196 million and is expected to reach 288 million in 2040. Also, the number of people with Diabetic retinopathy will grow from 126.6 million in 2010 to 191.0 million by 2030. In addition, it is estimated that there are 2.3 million people suffering from uveitis worldwide. Because of the anti-inflammatory properties of glucocorticoids (GCs), they are often used topically and/or intravitreally to treat ocular inflammation conditions or edema associated with macular degeneration and diabetic retinopathy. Unfortunately, ocular GC therapy can lead to severe side effects. Serious and sometimes irreversible eye damage can occur as a result of the development of GC-induced ocular hypertension causing secondary open-angle glaucoma. According to the world health organization, glaucoma is the second leading cause of blindness in the world and it is estimated that 80 million will suffer from glaucoma by 2020. In the current review, mechanisms of GC-induced damage in ocular tissue, GC-resistance, and enhancing GC therapy will be discussed.

PMID: 27388141

Epidemiology

Ophthalmology. 2016 Jul 1. [Epub ahead of print]

Validating the AREDS Simplified Severity Scale of Age-Related Macular Degeneration with 5- and 10-Year Incident Data in a Population-Based Sample.

Liew G, Joachim N, Mitchell P, Burlutsky G, Wang JJ.

PURPOSE: Most classification systems for age-related macular degeneration (AMD) were developed from patients in clinical trials. We aimed to validate the Age-Related Eye Diseases Study (AREDS) simplified severity scale of AMD classification using 5- and 10-year incident late AMD data from the population-based Blue Mountains Eye Study (BMES) cohort.

DESIGN: Comparative study of population-based cohort and clinical trial.

PARTICIPANTS: Blue Mountains Eye Study participants 40 to 97 years of age at baseline (n = 2134) and AREDS participants 55 to 80 years of age (n = 3640).

METHODS: In the BMES, AMD lesions were graded from stereoscopic color photographs and were classified according to the AREDS simplified severity scale. The AREDS simplified scale calculates a risk score based on the number of early AMD risk factors (large drusen and pigment abnormalities) in both eyes that can range from 0 to 4.

MAIN OUTCOME MEASURES: Five- and 10-year incident late AMD (presence of geographic atrophy or choroidal neovascularization).

RESULTS: The AREDS simplified scale performed similarly when applied to both the BMES population-based participants and the AREDS clinical trial-based participants in predicting 5- and 10-year incidence of late AMD. For scores 0 to 4, the 5-year incidence rates for the BMES compared with the AREDS were 0.2% versus 0.4%, 3.1% versus 3.1%, 12.1% versus 11.8%, 13.5% versus 25.9%, and 47.1% versus 47.3%, respectively. The corresponding 10-year incidence rates for the BMES compared with the AREDS were 0.7% versus 1.5%, 7.3% versus 8.4%, 36.6% versus 27.6%, 20.0% versus 52.7%, and 75.0% versus 71.4%, respectively.

CONCLUSIONS: The AREDS simplified severity scale classified late AMD risk levels similarly when applied to population-based and clinical trial samples. These results support the robustness of the AREDS simplified severity scale.

PMID: 27378016

Genetics

Mol Vis. 2016 Jun 24;22:718-33. eCollection 2016.

An ex vivo gene therapy approach in X-linked retinoschisis.

Bashar AE, Metcalfe AL, Viringipurampeer IA, Yanai A, Gregory-Evans CY, Gregory-Evans K.

PURPOSE: X-linked retinoschisis (XLRs) is juvenile-onset macular degeneration caused by haploinsufficiency of the extracellular cell adhesion protein retinoschisin (RS1). RS1 mutations can lead to either a non-functional protein or the absence of protein secretion, and it has been established that extracellular deficiency of RS1 is the underlying cause of the phenotype. Therefore, we hypothesized that an ex vivo gene therapy strategy could be used to deliver sufficient extracellular RS1 to reverse the phenotype seen in XLRs. Here, we used adipose-derived, syngeneic mesenchymal stem cells (MSCs) that were genetically modified to secrete human RS1 and then delivered these cells by intravitreal injection to the retina of the Rs1h knockout mouse model of XLRs.

METHODS: MSCs were electroporated with two transgene expression systems (cytomegalovirus (CMV)-controlled constitutive and doxycycline-induced Tet-On controlled inducible), both driving expression of human RS1 cDNA. The stably transfected cells, using either constitutive mesenchymal stem cell (MSC) or inducible MSC cassettes, were assayed for their RS1 secretion profile. For single injection studies, 100,000 genetically modified MSCs were injected into the vitreous cavity of the Rs1h knockout mouse eye at P21, and data were recorded at 2, 4, and 8 weeks post-injection. The control groups received either unmodified MSCs or vehicle injection. For the multiple injection studies, the mice received intravitreal MSC injections at P21, P60, and P90 with data collection at P120. For the single- and multiple-injection studies, the outcomes were measured with electroretinography, optokinetic tracking responses (OKT), histology, and immunohistochemistry.

RESULTS: Two lines of genetically modified MSCs were established and found to secrete RS1 at a rate of 8 ng/million cells/day. Following intravitreal injection, RS1-expressing MSCs were found mainly in the inner retinal layers. Two weeks after a single injection of MSCs, the area of the schisis cavities was reduced by 65% with constitutive MSCs and by 83% with inducible MSCs, demonstrating improved inner nuclear layer architecture. This benefit was maintained up to 8 weeks post-injection and corresponded to a significant improvement in the electroretinogram (ERG) b/a-wave ratio at 8 weeks (2.6 inducible MSCs; 1.4 untreated eyes, $p < 0.05$). At 4 months after multiple injections, the schisis cavity areas were reduced by 78% for inducible MSCs and constitutive MSCs, more photoreceptor nuclei were present (700/ μ m constitutive MSC; 750/ μ m inducible MSC; 383/ μ m untreated), and the ERG b-wave was significantly improved (threefold higher with constitutive MSCs and twofold higher with inducible MSCs) compared to the untreated control group.

CONCLUSIONS: These results establish that extracellular delivery of RS1 rescues the structural and functional deficits in the Rs1h knockout mouse model and that this ex vivo gene therapy approach can inhibit progression of disease. This proof-of-principle work suggests that other inherited retinal

degenerations caused by a deficiency of extracellular matrix proteins could be targeted by this strategy.

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Diet, lifestyle & low vision

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Molecular aspects of β , β -carotene-9', 10'-oxygenase 2 in carotenoid metabolism and diseases.

Wu L, Guo X, Wang W, Medeiros DM, Clarke SL, Lucas EA, Smith BJ, Lin D.

Abstract: Carotenoids, the carotenes and xanthophylls, are essential components in human nutrition. β , β -carotene-9', 10'-oxygenase 2 (BCO2), also named as β , β -carotene-9', 10'-dioxygenase 2 (BCDO2) catalyzes the asymmetrical cleavage of carotenoids, whereas β , β -carotene-15, 15'-monooxygenase (BCMO1) conducts the symmetrical cleavage of pro-vitamin A carotenoids into retinoid. Unlike BCMO1, BCO2 has a broader substrate specificity and has been considered an alternative way to produce vitamin A. In contrast to BCMO1, a cytoplasmic protein, BCO2 is located in the inner mitochondrial membrane. The difference in cellular compartmentalization may reflect the different substrate specificity and physiological functions with respect to BCMO1 and BCO2. The BCO2 gene mutations are proven to be associated with yellow color of skin and fat tissue and milk in livestock. Mutation in intron 2 of BCO2 gene is also supposed to be related to the expression of IL-18, a pro-inflammatory cytokine associated with obesity, cardiovascular diseases, and type 2 diabetes. Further, BCO2 is associated with the development of mitochondrial oxidative stress, macular degeneration, anemia, and hepatic steatosis. This review of the literature will mostly address recent updates regarding the role of BCO2 in carotenoid metabolism, and discuss the potential impacts of BCO2 protein and the mutations in mammalian diseases.

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Additive effect of age-related macular degeneration and glaucoma on quality of life.

Lin SC, Kakigi C.

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